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TECH CENTER 1600/2900 2 APPLICATION NO. ATTY. DOCKET NO. 09/917,789 1819.0030002/MAC/TSC FORM PTO-1449 APPLICANT DCT 282002 Lynch et al. FIRST SUPPLEMENTAL ORMATION DISCLOSURE STATEMENT FILING DATE GROUP 1493, 1647 July 31, 2001 U.S. PATENT DOCUMENTS EXAMINER DOCUMENT DATE NAME CLASS SUB-FILING DATE INITIAL CLASS NUMBER AΑ AΒ AC AD ΑE AF AG ΑH ΑI АJ AK FOREIGN PATENT DOCUMENTS EXAMINER INITIAL TRANSLATION DOCUMENT DATE COUNTRY CLASS SUB-NUMBER CLASS WO 96/30395 10/03/1996 WIPO AL1 A2 No WO 96/40737 12/19/1996 Yes WIPO AM1 No A1 07/15/1999 Yes WO 99/34781 WIPO No AN1 Α1 EP 1 026 251 08/09/2000 Europe A01 No A2 WO 01/53340 / 07/26/2001 WIPO AP1 No A2 OTHER (Including Author, Title, Date, Pertinent Pages, etc.) Bi, X., et al., "Lysomsomal Protease Inhibitors Induce Meganeurites and Tanglelike Structures in Entorhinohippocampal Regions Vulnerable to Alzheimer's AR 1 Disease," Exp. Neurol. 158:312-327, Academic Press (August 1999) Bi, X., et al., "Novel Cathepsin D Inhibitors Block the Formation of Hyperphosphorylated Tau Fragments in Hippocampus, " J. Neurochem. 74:1469-1477, AS 1 Lippincott Williams & Wilkens (April 2000) Bi, X., et al., "Rapid induction of intraneural neurofibrillary tangles in apolipoprotein E-deficient mice," Proc. Natl. Acad. Sci. USA 98:8832-8837, ΑT 1 National Academy Press (July 2001) DATE CONSIDERED EXAMINER **EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation in not in conformance and not considered. Include copy of this form with next communication to Applicant.

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| OCT 2 8 2002                               | JC98   | FORM         | PTO-1449                               |                                | ATTY. DOCKET NO.<br>1819.0030002/MAC/TS   | c                      | APPLI<br>09/91    | CATION NO     |                                    |
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| info                                       | MATIO  | N DIS        | SCLOSURE ST.                           | ATEMENT                        | FILING DATE<br>July 31, 2001  |                        | GROUP             | 1647          |                                    |
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|  | AM     | İ            |  |                                |   |                        |                   |               | Yes                                |
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|  |        |              | OTHER (Incl                            | uding Author                   | Title, Date, Pertinent  | t Pages                |                   |               | No                                 |
|  | AR     | 2            | Coogan, A.<br>SB203580 a<br>potentiati | N., et al., '                  | The P38 mitogen-activa<br>ne inhibitory effects o<br>dentate gyrus <i>in vitr</i> | ted prote<br>f interle | in kina<br>ukin-1 | 3 on long     | -term                              |
| CQC  | AS     | 2            | cholestero                             | l level, age,                  | Interactions of apoliped and sex in prediction ogy 45:1092-1096, Lippin           | of Alzhe:              | imer's            | disease:      | A case-                            |
| (30)                                       | AT     | 2            | Internatio                             | nal Search Ro<br>June 5, 2002. | port for International  | Applicat:              | ion No.           | . PCT/USO     | 1/23894_                           |
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|   | AL       |                |                          |                                 |  |                         |                |                                       |                   | Yes<br>No                             |
| (30)  | AM2      | WO 00          | 0/21550 A2               | 04/20/2000                      | WIPO   |                         |                |                                       |                   | Yes<br>No                             |
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|   | AP       |                |                          |                                 |  |                         | _              |                                       | <u> </u>          | Yes<br>No                             |
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| C30   | AR       | <u>3</u>       | Icvtoskelet              | al disruption:                  | ., "Hyperphosphorylat<br>s in mice overexpressi<br>USA 97:2910-2915, Nat         | ing human n'            | 25 an          | antimate                              | ~ ~ f             | cdk5,"                                |
| 630   | AS       | 3              | Akiyama, H<br>21:383-421 | ., et al., "I<br>, Elsevier Sc: | nflammation and Alzhe<br>ience, Inc. (May/June                                   | imer's disea            | ase," i        | Neurobic                              | l. Agi            | ng                                    |
| CS  | AT       | <u>3</u>       | Hippocampu               | s: Evidence fo                  | duction of β-Amyloid-(<br>or a Concomitant Loss<br>citotoxin," <i>Exp. Neuro</i> | of Synantic             | Prote          | ine and                               |                   | Inc.                                  |
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Page 2 of 15 ATTY. DOCKET NO. APPLICATION NO 1819.0030002/MAC/TSC 09/917,789 FORM PTO-1449 APPLICANT Lynch et al ATION DISCLOSURE STATEMENT FILING DATE GROUP July 31, 2001 1493 FTRADE v.s. PATENT DOCUMENTS EXAMINER INITIAL DOCUMENT DATE NAME SUB-CLASS FILING DATE NUMBER CLASS AA AB AC AD ΑE AF AG AΗ ΑI АJ ΑK FOREIGN PATENT DOCUMENTS EXAMINER INITIAL DOCUMENT DATE COUNTRY CLASS SUB-TRANSLATION NUMBER CLASS Yes AT. No Yes AM No. Yes AN No Yes ΑO No Yes ΔP No OTHER (Including Author, Title, Date, Pertinent Pages, etc.) Bednarski, E., and Lynch, G., "Cytosolic Proteolysis of  $\,\tau$  by Cathepsin D in Hippocampus Following Suppression of Cathepsins B and L, " J. Neurochem. 67:1846-AR 4 1855, Lippincott-Raven Publishers (1996) Bednarski, E., et al., "Suppression of Cathepsins B and L Causes a Proliferation of Lysosomes and the Formation of Meganeurites in Hippocampus, " J. Neurosci. AS 4 17:4006-4021, Society for Neuroscience (1997) Bednarski, E., and Lynch, G., "Selective suppression of cathepsin L results from elevations in lysosomal pH and is followed by proteolysis of tau protein," ΑТ 4 Neuroreport 9:2089-2094, Rapid Science, Ltd. (1998) EXAMINER DATE CONSIDERED 217104 **EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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| C20)                | AS       | <u>5</u>   | Hyperphosp   | horylated Tau  | Fragments in Hippoca                    | ampus." J.   | e Forma<br>Neuroch | tion of hem. 74:1 | L469-1477,               |
| (3)                 | АТ       | <u>5</u>   | includes t.  | he phosphoryla | ation of two serine-p                   | oroline moti | fs ups             | tream of          | the                      |
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| C3>                 | AR       | <u>6</u>   | Amyloid F              | recursor Pr                | otei            | W.L., "Cholesterol<br>n," <i>J. Biol. Chem.</i><br>ar Biology, Inc. (19                         | 271:4436-4               |                          |  |                             |
| ري (                | AS       | <u>6</u>   | Implicati              | ons for Cho                | lest            | in, J.L., "Lipoprote<br>erol Deposition in A<br>ws, Inc. (1983)                                 | ein Metabo<br>Atheroscle | olism i<br>erosis,       | n the Macro<br>" Ann. Rev                        | ophage:<br>riew Biochem.    |
| 03                  | АТ       | <u>6</u>   | Associate<br>Resonance | ed with Neur<br>Energy Tra | ofib<br>nsfe    | rotubule-Affinity R<br>rillary Tangles in A<br>r Study," <i>J. Neurop</i><br>Neuropathologists, | Alzheimer<br>athol. Exp  | Brain:<br>p. <i>Neur</i> | A Fluores<br>col. 59:966                         | cence                       |
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|   | AO         |              |                |  |  |                                |                             |                          | Yes<br>No             |
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| 650                                     | AR         | 7            | between Pa     | m, P., et al<br>thogenic Mecl<br>ress (1998) | ., "Inflammation<br>nanisms and Clini                        | and Alzheimer<br>cal Expressio | r's Disea<br>n," <i>Exp</i> | se: Relati               | onships<br>154:89-98, |
| 0                                       | AS         | <u>7</u>     | Alzheimer'     | s Disease and                                | ., "Temporal Cort<br>I Is Negatively Co<br>39, Academic Pres | orrelated wit                  | sin mRNA<br>h the Se        | . Is Reduce<br>verity of | ed in<br>Dementia,"   |
| (3 <sup>)</sup>                         | AT         | <u>7</u>     | hippocampa     | l formation i                                | "Loss of synaptop<br>s an early phenor<br>cience, Ltd. (199  | menon in Alzh                  | munoreac<br>eimer's (       | tivity in<br>disease,"   | the<br>Neurosci.      |
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| C300                | AR (     | <u>8</u>                 | Hoffman, K<br>Neurosci.              | .B., et al., 'Lett. 250:75-7 | "β-Amyloid increases<br>78, Elsevier Science                         | s cathepsin<br>e Ireland, L | D level          | ls in hipp<br>998) | pocampu           | S,"         |
| 03                  | AS       | <u>8</u>                 | Amyloid β-1                          | Peptide in Bra               | "Modulation of Secre<br>ain by Cholesterol,"<br>ochemistry and Molec | " J. Biol. C                | hem. 2           | 73:16576-          | otein a<br>16582, | nd<br>The   |
| (3)                 | AT :     | <u>8</u>                 | Huang, D.Y. serine <sub>262</sub> ph | nosphorylation,              | poE3 binding to tau<br>," Neurosci. Lett.                            | tandem repe                 | at I is<br>Elsev | abolishe           | ed by take        | au<br>land, |
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FORM PTO-1449

RMATION DISCLOSURE STATEMENT

ATTY. DOCKET NO. 1819.0030002/MAC/TSC

APPLICATION NO. 09/917,789

APPLICANT Lynch et al

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| ري                | AR          | Alzheime              | .A., et al.,<br>r's Disease,<br>er 1999) | "cAMP-Dependent Prot" J. Neurosci. 19:74       | tein Kinase Phosph<br>86-7494, Society 1 | orylations<br>for Neurosci | on Tau in<br>ence |
| (N)               | AS          | Jick, H. The Lanc     | , et al., "S<br>et (November             | tatins and the risk o                          | of dementia," The                        | Lancet 356:                | 1627-1631,        |
| 0                 | <b>)</b> AT | 9 Manser,<br>and Rac1 | E., et al.,<br>," Nature 36              | "A brain serine/thred<br>7:40-46, Macmillan Ma | onine protein kina<br>agazines, Ltd. (19 | se activate                | d by Cdc42        |
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|   | Mercken, Mer | M., <i>et al</i> ., "<br>an tau, fetal           | Differential sensitivi                                 | ty to proteoly:                   | sis by brain              | n calpain of<br>Elsevier |
| AT 1  | <u>10</u>   Cellular C   | Cholesterol H                                    | omeostasis," <i>J. Biol.</i>                           | Chem. 275:3844                    | 5-38451, The              | cers<br>e American       |
|   | Miller, C.   | C.J., et al.<br>ment side arms                   | , "Alzheimer's paired<br>s," <i>EMBO J.</i> 5:269-276, | helical filamer<br>IRL Press, Ltd | nts share eg<br>1. (1986) | oitopes with             |
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| CSN  | AR   | 11           | Cathepsins   | D, E, B, and                            | L in the Rat Brain Tissu                                  | Activiti<br>les," <i>E</i> 2 | es and<br>xp. Ne | l Locali:<br>urol. 12 | zations of<br>6:119-128, |
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| 03                   | AR               | <u>12</u> | Pei, JJ.<br>in Brains<br>Exp. Neuro  | , et al., ":<br>Staged for 1<br>ol. 58:1010- | Distr<br>Alzhe | ibution of Active G<br>imer Disease Neurof        | lycogen<br>ibrillar | Synthas            | es." J. N              | Jeuropathol                |
| (3)                  | AS               | <u>12</u> | Developmen   | t of Alzheir                                 | mer's          | Disease in Memory-                                | Impaired            | Predic             | tor of the             | e<br>YAMA                  |
| 03                   | АТ               | <u>12</u> | Pathology  | ın a Transge                                 | "Hyp<br>enic 1 | ercholesterolemia A<br>Mouse Model," <i>Neuro</i> | ccelerat            | es the .is. 7:32   | Alzheimer<br>1-331, Ac | 's Amyloid<br>ademic Press |
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|                     | AO           |            |                      |   |   |                                |                 |                | Yes<br>No  |
|                     | AP           |            |                      |   |   |                                |                 |                | Yes<br>No  |
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| (B)                 | AR           | <u>13</u>  |                      |   | nflammation and Al:<br>1-686, Elsevier Sc:                  |                                |                 | athogenesi     | is,"   |
| CS                  | AS           | <u>13</u>  | Activation Type C Mi | n of Mitogen-a<br>ce," <i>J. Biol</i> . | "Site-specific Phosactivated Protein F<br>Chem. 276:10314-1 | Kinase (MAPK)<br>0319, The Ame | in Bra<br>rican | ains of Ni     | emann-Pick                                       |
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| (3)   | AR             | <u>15</u>   | von Bergen, M., et al., "Assembly of $\tau$ protein into Alzheimer paired helical filaments depends on a local sequence motif ( $^{306}\text{VQIVYK}^{311}$ ) forming $\beta$ structure," Proc. Natl. Acad. Sci. USA 97:5129-5134, National Academy Press (May 2000) |  |              |  |        |                            |  |               |  |  |
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